Improvement in diastolic intraventricular pressure gradients in patients with HOCM after ethanol septal reduction

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HOCM patients have preserved LV systolic function, but their diastolic function, in particular, LV relaxation, is frequently impaired (14, 15, 22). Doppler echocardiography is commonly used to evaluate diastolic function in these patients. However, standard Doppler indexes of LV filling are not always accurate in assessing relaxation in HOCM patients because these indexes are also affected by preload (23). Recently, color M-mode Doppler has been utilized for noninvasive evaluation of LV relaxation (1, 15, 23, 24). We have demonstrated that in contrast to pulsed Doppler LV filling indexes, color M-mode Doppler propagation velocity ($V_p$) is relatively independent of preload (8). We have also demonstrated that data from color M-mode Doppler may be analyzed by the Euler equation to calculate diastolic intraventricular pressure gradients (IVPG) (10), which represent diastolic suction force originally described by Katz (11).

The aims of the present study were, therefore, to 1) validate the noninvasive measurement of IVPG in patients with HOCM, 2) apply this methodology to determine whether the IVPG increases in HOCM patients after ESR, and 3) determine whether these changes correlate with the reduction in LVOT obstruction and improvement in symptoms.

MATERIALS AND METHODS

Patient group 1: invasive validation of IVPG. We prospectively validated the noninvasive determination of IVPG in a group of 10 patients (age 51.3 ± 3 yr, 4 male) undergoing septal myectomy. The protocol was approved by the Institutional Review Board of the Cleveland Clinic Foundation. All patients in the surgical group had general anesthesia induction, median sternotomy, and pericardiectomy. A transesophageal echocardiogram (Acuson Sequoia 512 equipped with a multiplane transducer) was performed in the operating room. Color M-mode Doppler was obtained in sinus rhythm using...
standard technique (8). Care was taken to optimize the temporal and velocities resolution. Data were obtained before and after septal myectomy while the patients were off the bypass pump. The images were stored digitally for future analysis.

The color Doppler M-mode images were processed to extract the velocity information from the raw image data using customized software (LabVIEW, National Instruments; Austin, TX). The software allows the end user to calibrate the image file and to identify the regions within the image where velocities are aliased. Once identified, a dealiasing algorithm was used to convert the color pixels into true velocities \( v(s,t) \), representing the velocity at point \( s \) in the LV inflow tract and \( t \) during diastole) using the Nyquist limit stored on the individual color M-mode image.

The theoretical background for noninvasive estimation of the IVPG has been described previously by our group (10). Briefly, the Navier-Stokes differential equations for non-compressible fluids were simplified by assuming that blood flow is imaged along a streamline. This allows us to obtain a noninvasive estimate of the IVPG utilizing both the convective and inertial contribution of the mitral inflow velocities (10).

Invasive determination of the intraventricular gradients was performed using a high-fidelity triple sensor pressure transducer (Millar Instruments; Houston, TX) introduced into the LV as shown schematically in Fig. 1. The final position was verified by transesophageal echo visualization and by confirming the chamber-appropriate waveforms. Pressure signals from LA, LV base, and LV apex were acquired and amplified simultaneously with the echocardiographic recording of the color M-mode Doppler using a customized data acquisition and analysis software (LabVIEW, National Instruments) as described (10). The data recorded were rounded to a multiple of 0.5 mmHg given the limits for expected accuracy of Millar catheter data. Data were recorded and stored for future off-line analysis.

To obtain the pressure gradient information, the LV basal and apical pressure curves were automatically aligned in time with color M-mode Doppler data by using a time marker signal generated by the software; this time marker also appeared on the color M-mode Doppler echocardiographic images. The pressure curves were manually aligned at the end of long diastatic intervals. The IVPG were determined by subtracting the early diastolic LV apical pressure from that of the LV basal pressure (IVPG = LV\textsubscript{base} - LV\textsubscript{apex}). All beats demonstrated a positive difference in early diastole (i.e., every beat generated an intraventricular pressure gradient that was positive in early diastole). Three representative beats were averaged to obtain the final IVPG value that was used in the statistical analysis to compare with the noninvasive data. The IVPG were determined at baseline and immediately after myectomy; thus each patient provided two independent data measurements for analysis.

**Patient group 2:** determination of IVPG before and after ESR. To define the effect of ESR on the IVPG, a review of echocardiographic data pre- and post-ESR was undertaken in a second group of 19 patients (age 63.6 ± 3 yr, 6 male) with HOCM who had septal reduction between 1998 and 2000. Patients were selected to undergo ESR if they were symptomatic on maximal medical therapy. In this group, the LVOT gradient at baseline was 61.8 ± 10 mmHg and amyl nitrate-provoked LVOT gradient was 113.9 ± 26.7 mmHg; in all cases, this was secondary to systolic anterior motion of the mitral leaflet. All subjects had asymmetric septal hypertrophy at baseline. Inclusion criteria were normal sinus rhythm and absence of mitral valve stenosis or mechanical mitral valve prosthesis. Also, these patients had to have a baseline and followup echocardiogram (5.6 ± 1.2 mo) that included color M-mode Doppler. The protocol was approved by the Institutional Review Board of the Cleveland Clinic Foundation.

A single operator (E. M. Tuzcu) performed the septal reduction in the cardiac catheterization laboratory. A femoral artery transcutaneous approach was used. The first septal perforator was identified. Contrast echocardiography (delivered through the catheter) was used to ensure that the catheter was properly positioned and that the myocardial territory supplied by the vessel was appropriate for the procedure. If the vessel was inappropriate, another septal perforator was instrumented and assessed. With a target vessel identified, ethanol (2–3 ml) was subsequently injected.
through the catheter distal to the balloon to achieve a controlled reduction of the basal septal myocardium.

Clinical follow-up. New York Heart Association (NYHA) functional status was determined clinically for each patient prior to ESR and at follow-up. Patients also underwent a standard exercise stress test before ESR and at follow-up; the amount of work and the total exercise time were recorded. Medication usage was recorded before and after ESR. A permanent pacemaker was inserted after ESR if patients demonstrated a high degree of atrioventricular nodal blockade.

Echocardiographic examination. Transthoracic echocardiographic studies were performed before and after ESR (mean ± SD 5.6 ± 1.2 mo) using an Acuson Sequoia imaging ultrasound system equipped with 1.7–3.5 MHz transducer and harmonic imaging. Standard parasternal and apical views were obtained (20).

Apical four-chamber view was used to obtain the color M-mode Doppler tracing. The baseline was shifted as needed to obtain a sharp border of the color velocity map (16), and the $V_p$ was measured as the slope of the first aliasing velocity of the early filling waveform from the mitral valve tips to 4 cm into the LV cavity (6). This method of measuring the $V_p$ was chosen for several reasons: the standardization of this method is simple, it is highly reproducible, and it has been validated in our laboratory. It is well established that different methods of obtaining the $V_p$ will effect the results; thus the same method was used to obtain $V_p$ at all times (21).

Subsequently, the IVPG were calculated off-line from the color M-mode image as previously described (8). Note that the value of $V_p$ does not per se play a role in calculation of the IVPG because all the velocities from the color map are extracted to obtain the IVPG value. A representative image of the color M-mode Doppler and mitral inflow pulse Doppler data before and after ESR are shown in Fig. 2.

LV end-diastolic and end-systolic dimensions and septal and posterior wall thickness were obtained from two-dimensional images per previously published guidelines (20). The early filling ($E$) and atrial contraction ($A$) velocities and deceleration time of the $E$ velocity were obtained from mitral inflow pulsed Doppler. Tissue Doppler imaging was used to obtain early diastolic ($E_a$) velocities at the septum of the mitral annulus. The ratios $E/E_a$ and $E/V_p$, previously proposed as indexes of filling pressure, were calculated (6, 15). The severity of mitral regurgitation (MR) was determined from color Doppler based on the MR index described (25).

Studies were stored digitally for analysis. A single observer who was blinded to the temporal relationship of the studies analyzed the baseline and followup echocardiograms (A. Rovner).

To obtain a normal range for IVPG, a cohort of normal volunteers was recruited via an advertisement. The exclusion criteria were any significant cardiac or valvular disease as well as history of any significant arrhythmia. All subjects signed an informed consent. A limited echocardiogram (CMM) and mitral inflow pulse Doppler before and after (C and D, respectively) ethanol septal reduction (ESR) were obtained and analyzed as described above. SPSS version 10.0 for Windows (SPSS; Chicago, IL) was used for all statistical analyses. Data are presented as means ± SD. To test the hypothesis that the improvement in diastolic relaxation by reduction of the LVOT systolic gradient after ESR can be assessed by noninvasive determination of IVPG, we compared the pre- and postdata using the Student’s $t$-test for continuous variables. The relationship between the change in IVPG and changes in LVOT gradient was determined by Pearson correlation and simple linear regression method. Spearman correlation was used to compare the IVPG and LVOT systolic gradients with NYHA functional class.

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Fig. 2. Representative images of the improvement in color M-mode Doppler (CMM) and mitral inflow pulse Doppler before (A and B, respectively) and after (C and D, respectively) ethanol septal reduction (ESR). Baseline intraventricular pressure gradient (IVPG) = 1.2; IVPG after ESR = 3.2 mmHg.
Patient group 1: validity of noninvasively determined IVPG. The color M-mode was performed successfully in all cases. Technical failure of the multisensor Millar catheter measurements (catheter malfunction in one case and inadequate or loss of pressure waveform in two cases) resulted in the elimination of 6 data points; thus the analysis was performed on 14 of 20 possible data sets. The mean IVPG determined from the color M-mode Doppler data before myectomy was 3.0 ± 0.8 mmHg, whereas the same mean IVPG determined invasively was 2.9 ± 0.8 mmHg [P = not significant (NS)]. The mean IVPG determined from the color M-mode Doppler data immediately postmyectomy was 3.3 ± 0.5 mmHg, whereas the same mean IVPG determined invasively was 3.4 ± 0.8 mmHg (P = NS). A good correlation between the color M-mode-determined IVPG and invasively determined IVPG was observed premyectomy (ρ = 0.95, P < 0.01) as well as postmyectomy (ρ = 0.81, P < 0.01). Global ρ was 0.8, P < 0.01 (Fig. 3A). Bland-Altman analysis of the agreement between these two methods before and after myectomy is demonstrated in Fig. 3B.

Patient group 2: effects of ESR. At follow-up after ESR, patients exhibited a decrease in both baseline LVOT systolic gradient (62 ± 10 to 29 ± 5 mmHg, P < 0.001) and amyl nitrite-provoked LVOT systolic gradient (113.9 ± 26.7 to 65.7 ± 29.9 mmHg, P < 0.001). Table 1 summarizes the changes in clinical status and exercise capacity in patients at baseline and after ESR. There was a statistically significant decrease in baseline symptoms as well as an improvement in NYHA functional class. Exercise capacity improved as indicated both by the amount of work and total exercise time. The number of medications that patients were taking did not change significantly after ESR. Five patients required insertion of a permanent pacemaker. The LVOT systolic gradient had a direct correlation with the NYHA functional class, and improvement of the diastolic function (as demonstrated by improvement in IVPG) correlated well with the improvement in NYHA (Fig. 4). ESR resulted in improvement of the index of the MR severity (from 2.1 ± 0.2 to 1.4 ± 0.1, P < 0.01, using a 4-point scale).

Changes in LV dimensions in patients after ESR are shown in Table 2. ESR produced a significant reduction in intraventricular septal thickness in the region of the reduction. The posterior wall decreased in size as well indicative of the positive remodeling of the LV, but this change did not reach statistical significance.

Improvement of diastolic function after ESR. A summary of the changes in diastolic Doppler indexes is shown in Table 3. There was a decrease in peak E velocity and an increase in peak A velocity at follow-up after ESR, resulting in a significant reduction in the E-to-A ratio. Mitral inflow deceleration time did not change at follow-up. There was a significant increase in Vp and a similar trend in Ea.

Reduction in estimate LA pressure was also reflected in the reduction of LA area (Table 2). E/Ea ratio that can also be used to estimate LV filling pressures demonstrated similar results (data not shown).

IVPG in patients after ESR. Adequate color Doppler M-mode images were obtained in all 19 patients at baseline and at follow-up. The means ± SD for intraobserver variability of determining the IVPG was −0.05 ± 0.06 mmHg, and the correlation between measurements was 0.9 (P < 0.01). IVPG at baseline was 1.5 ± 0.2 mmHg and increased to 2.6 ± 0.3 mmHg (P < 0.001) at follow-up (Fig. 5). As shown in Fig. 5, the majority of patients analyzed experienced an increase in IVPG after undergoing ESR. These values are sim-
and after septal oblation

Table 2. Change in LV wall size and PCWP before and after septal ablation

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Followup</th>
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<tbody>
<tr>
<td>Septum, mm</td>
<td>2.3 ± 0.09</td>
<td>1.9 ± 0.05*</td>
</tr>
<tr>
<td>Posterior wall, mm</td>
<td>1.4 ± 0.05</td>
<td>1.3 ± 0.05</td>
</tr>
<tr>
<td>LA area, cm²</td>
<td>31.4 ± 2</td>
<td>26.2 ± 1.5†</td>
</tr>
<tr>
<td>Estimated PCPW, mmHg</td>
<td>16.2 ± 1.1</td>
<td>11.5 ± 0.9†</td>
</tr>
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Values are means ± SD. LA, left atrium; LV, left ventricle; PCPW, pulmonary capillary wedge pressure. *P < 0.01 vs. baseline; †P < 0.001 vs. baseline.

Fig. 4. A: relationship between the New York Heart Association (NYHA) functional class and LV outflow tract (LVOT) systolic gradient (ρ = 0.56, P < 0.01). B: relationship between the NYHA functional class and diastolic IVPG (ρ = −0.42; P < 0.01).

Similar to those obtained from normal individuals (mean age 34.6 ± 8.5 yr) in our laboratory (2.02 ± 0.94 mmHg).

The change in the IVPG correlated significantly with the change in the LVOT gradient (r = 0.6, P < 0.05) (Fig. 6). The change in MR severity also correlated well with the increase in the IVPG (ρ = 0.7, P < 0.01). The increase in IVPG correlated well with the observed increase in Vp (r = 0.5) and exhibited an inverse correlation with the decrease in E/Ea (r = −0.5) and in E/EA (r = −0.7, all P < 0.01). There was a significant inverse correlation between the IVPG and the NYHA functional class (ρ = −0.42, P < 0.01; Fig. 4B).

Five patients required permanent pacing for high-degree atrioventricular block. The IVPG in this group at baseline was 1.1 ± 0.8 mmHg and it improved after ESR to 2.2 ± 1.2 mmHg. The Vp followed the same trend (43.2 ± 22.2 to 82.5 ± 36.0 cm/s). This was not statistically different from the group that did not get a pacemaker after the procedure. The provoked LVOT gradient was 93 ± 33 mmHg and it decreased to 73.6 ± 44.3 mmHg, again not statistically different from the group without pacing. The percent change of the LVOT gradient correlated well with that of the IVPG, similar to the group without pacing (r = 0.7, P < 0.001). The improvement in diastolic function was seen in both E/A (2.7 ± 1.7 to 0.8 ± 0.2) and E/Vp (2.6 ± 0.7 to 1.1 ± 0.6), which were, again, not statistically significant compared with the group without the pacemaker. All of the above changes were significant to P < 0.01 between baseline and post-ESR.

DISCUSSION

Our results demonstrate that noninvasive measurement of IVPG from color M-mode Doppler data can be obtained accurately in patients with HOCM. These IVPG increase after ESR and correlate with functional class and with the reduction in LVOT systolic gradients.
The presence of regional pressure differences in the LV and their relation to LV relaxation and suction has long been known. Courtois and colleagues described the presence of diastolic regional pressure differences and also demonstrated a reduction in diastolic IVPG with ischemia in a canine model (2, 3). Despite the apparent importance of IVPG, they have never been utilized in clinical cardiology, due to the complexity of their acquisition. Fortunately, our group has recently demonstrated that IVPG can be accurately estimated by applying the Euler equation to color M-mode flow propagation data, greatly expanding the potential application of this technique clinically (5, 10). Subsequently, we demonstrated an immediate increase in diastolic IVPG that correlated with the improvement in LV function in patients undergoing coronary bypass surgery (5).

In this study, we validated the application of our noninvasive method to obtain the IVPG in patients with HOCM. In many ways, HOCM represents a worst-case scenario for application of the Euler equation to transmitral color M-mode flow data, given the impact that altered LV geometry may have on mitral inflow independent of any changes in diastolic function. That this approach works in HOCM patients is encouraging in that it may be applicable in a broad range of cardiac patients. The small number of subjects used in the validation part of our study is reflective of the difficulty in proper positioning of the Millar catheter in the LV in patients with HOCM. Nonetheless, our results demonstrated a good correlation between the invasive and the noninvasive data. Our group has demonstrated the validity of this method in a larger series of patients without septal hypertrophy (5).

**Diastolic function in HOCM.** The diseased cardiac myocytes and fiber disarray account for the poor diastolic performance and increase in LV filling pressures in HOCM. In addition, the increase in afterload caused by the LVOT obstruction in HOCM further impairs LV relaxation, thus explaining the improvement observed after septal reduction with ethanol. Nishimura et al. (5) showed that the transmitral E/A Doppler velocity ratio has a limited utility in patients with HOCM. This is not surprising because the LV filling dynamics and the mitral inflow geometry in patients with HOCM are very different from a normal size heart. Nagueh et al. (15) demonstrated that newer indexes of diastolic function, namely, V_p and E_a, were better indicators of diastolic function in these patients. It has been shown that V_p correlates well with the time constant of isovolumic relaxation τ in patients with and without HOCM (18). In our study group, the observed reduction in the E-to-A ratio could be interpreted as either a decrease in preload or worsening of the LV relaxation. Yet, the color M-mode Doppler V_p significantly increased after ESR, strongly indicating the improvement in relaxation. We go further in that we use the color M-mode Doppler data to their fullest potential to obtain quantitatively the LV regional pressure difference that represents the improvement in diastolic suction.

Our study confirms septal size reduction and improvement in diastolic function in patients with HOCM after septal reduction with ethanol. This is evident using both conventional diastolic parameters as well as measurements of IVPG. We also demonstrated a decrease in LA area, E/V_p, and E/E_a (albeit not statistically significant) after septal ablation, indicating a decrease in LV filling pressure. The significance of these findings must relate to the overall LV remodeling after the reduction of the LVOT obstruction by septal ablation. This together with the trend in reduction of the posterior wall thickness—although not to a statistically significant level—is consistent with the notion that some of the LV hypertrophy is secondary to the increase in afterload caused by the LVOT obstruction. The diastolic function improvement appears to be related to this phenomenon as well.

We have demonstrated an important relationship between the IVPG and overall clinical status of these patients. Improvement in exercise capacity, decrease in systolic LVOT gradient, and decrease in MR severity correlated well with improvement in IVPG. There were several patients in whom the IVPG gradient decreased after the procedure. The LVOT gradient did not worsen in this group of patients. The E/A ratio and the E_a did improve in this patient group. This likely represents the multifactorial effects of this disease on diastolic function where IVPG gradient does not fully represent the extent of improvement in diastolic function.

Garcia et al. (7) and others (12, 13) have demonstrated that pulsed Doppler early filling deceleration time relates to the LV operating stiffness. In this study population, however, deceleration time did not change after ESR. This is most likely secondary to the complex dynamic interplay between relaxation, preload, and operating stiffness. At baseline, these patients have a higher preload and thus a stiffer ventricle and impaired relaxation, as demonstrated by both conventional and newer diastolic indexes already described. After ESR, their relaxation improves; however, they also operate at less preload and presumably on a less...
stiff portion of their diastolic pressure-volume curve. This interplay resulted in no net change in the deceleration time.

**Advantages of the IVPG.** The determination of diastolic function using IVPG offers several advantages over the conventional diastolic parameters that are currently in clinical use. Pulsed Doppler techniques measure velocity information at one point in space and at one point in time; the IVPG are derived from the color M-mode Doppler, which provides velocity information along the whole scan line in time and space. Currently, there are two common ways to report the information that is obtained from the color M-mode Doppler: the Vp and the time delay of the maximum velocity (6). To overcome these manual empirical measurements, we offer the computerized calculation of the IVPG.

IVPG is an adequate tool to evaluate diastolic function in patients with HOCM as evident from our data. Contrary to standard pulsed mitral Doppler velocities, color M-mode Doppler is not affected by preload (8). These data are highly reproducible and can be followed in time. The ability to integrate the continuum of the velocities from LV base to LV apex can produce the pressure maps that allow for a noninvasive determination of LV filling pressures.

**Limitations of the study.** The critical assumption in measuring the IVPG is that the M-mode scanline is aligned with the streamline of the blood inflow through the mitral valve. Given the complicated geometry of the LV with an asymmetric septum, this assumption may not be correct. However, Greenberg et al. (10) have previously shown that precise alignment of the scanline is not necessary; in fact, the error in calculating the IVPG was <0.26 mmHg even if the scanline was displaced more than halfway to the edge of the valve or misaligned by up to 20°.

A technical limitation exists in acquiring good images of the color M-mode. It is more true in this patient population due to the geometrical three-dimensional complexity of the mitral inflow. Several techniques were proposed, namely, changing the Nyquist limits to increase aliasing and changing the baseline shift to provide a sharp border of the color map.

Determination of IVPG using the high-fidelity pressure transducers had several technical difficulties. The small hyperdynamic LV presented a challenge for the surgeon to properly position the catheter. Also, the pressure waves were distorted if the catheter had contact with the LV walls or the mitral valve; thus several waveforms could not be analyzed in our study for these reasons. Nevertheless, when the representative waveforms were analyzed, a good correlation was observed.

There was no invasive data in the ESR patient group to demonstrate the improvement in diastolic function. However, we examined multiple previously validated noninvasive parameters that are known to correlate with the diastolic performance. Improvement in both LA size and pressure, as well as improvement in Doppler echocardiographic indexes demonstrate an improvement in diastolic function after ESR.

Given the small size of our patient population and the challenge of obtaining good quality data, further studies are needed to validate our conclusions. Nevertheless, our correlation between the increase in IVPG and decrease in LVOT gradient and the increase in other diastolic parameters validate the observed physiologic relationships. IVPG that are obtained in a noninvasive manner can be used in clinical practice as yet another index of diastolic function that will help better understand this complex phenomenon.

Portions of this study were presented at the 2002 American College of Cardiology Meeting at the Young Investigator Competition.

**DISCLOSURES**

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